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07/542,149	06/22/90	KEITH J	

EXAMINER	
BUGAISKY, G	

ART UNIT	PAPER NUMBER
1814	13

DATE MAILED: 04/03/92

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/19/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 2-10 are pending in the application.
   Of the above, claims 2-4 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 5-10 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1814.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. As pointed out in the response to the initial Office Action, the specification defines "substantially reduced", which is 1000 fold less than wild type or negligible compared to wild type. Table Six (p 47a) lists the enzymatic activity of various mutants. Wild type enzyme yields about 24,000cpm, whereas the mutants with the least activity yield about 750 cpm. This is only an approximately 30-fold reduction, not the 1000 fold of the definition. The disclosure fails to reveal any mutants with a substantially reduced activity (i.e., yielding about 24 cpm).

Even if the specification were enabled with regards to DNA encoding a polypeptide with substantially reduced activity, the scope of the claims is not commensurate with the enablement. It

is clear that the disclosed 4-1 mutant (arg9→lys9) has a reduced enzymatic activity (although not substantially reduced, as discussed above) and binds a neutralizing antibody. The Examiner feels that it would not be undue experimentation to test the effects of mutations allowing the other 18 amino acids at position 9. Most likely, all would show reduced activity; because of their side groups, some might interfere with the epitope recognized by protective antibodies. It would be undue experimentation however, to extend the claims to include the region bounded by tyr8 and pro14, because in addition to the 18 other possible mutations at position 9, one would have to test 20^6 single codon mutations alone, in addition to an incalculable number of mutations affecting several codons. One skilled in the art may be quite diligent, but it is an undue burden to determine whether any mutation(s) yield a polypeptide with the two desired characteristics. Furthermore, the Examiner wishes to point out that the Applicants have demonstrated the properties for only mutant 4-1, and not that any truncated S_1 gene with a mutation at arg9 will suffice. It seems logical to conclude that a polypeptide encoded by the latter gene would demonstrate a reduced activity, but it is not apparent that such a polypeptide would be recognized by a immunoprotective antibody. Applicants have not clarified the features of the epitope recognized by a neutralizing antibody and it is not inconceivable that such an antibody recognizes a specific tertiary conformation, rather than

an absolute sequence. If this the case, then even though the antibody clearly binds to the region between aa8-15, the folding of the -COOH terminal portion of the protein may be important in the specific configuration the amino terminus presents to the antibody. No evidence has been presented regarding the minimum fragment or portion of DNA which encodes a polypeptide of the desired characteristics, thus no guidelines have been presented with which one could predict success with any sequence encoding less than the entire -COOH terminus. One skilled in the art would thus be faced with undue experimentation in order to determine the metes and bounds of the invention.

Claims 5-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The rejection under 35 U.S.C. §102(a) based on Burnette, et al. (Science) is withdrawn due to the Applicant's declaration under 37 C.F.R. 1.131.

The rejections (and provisional rejection) under 35 U.S.C. § 103 based on Burnette, et al. (J. Cell. Biochem.) are withdrawn. The reference points out the importance of a.a. 8-14 of the S_1 subunit in both enzymatic activity and binding of neutralizing antibodies. One however could not have a reasonable expectation of success in obtaining a specific mutant pertussis toxin gene

encoding a protein with a decreased ADP-ribosyltransferase activity which nevertheless reacts with a neutralizing antibody.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. Bugaisky, Ph.D. whose telephone number is (703) 308-4201.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM-1 Fax Center number is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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March 31, 1992

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180